Linking genetics with biology in disease research: an interview with Nick Hastie

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Professor Nick Hastie is Director of the MRC Human Genetics Unit in Edinburgh, a centre originally famous for early studies of chromosome biology. He is also Director of the newly formed Institute of Genetics and Molecular Medicine, which includes the Human Genetics Unit. In addition to overseeing the work on cancer and developmental genetics in his own lab, he is involved in a number of large-scale genetic studies aimed at uncovering genetic risk factors for various human diseases.

Nick Hastie was born in the village of Rhos-on-Sea, North Wales, and as a child never once imagined becoming a scientist. Although he claims that social acumen and a good mentor helped get his career off the ground initially, as an independent scientist he has made countless contributions to many areas of research, ranging from virology and telomere biology to kidney cancer and population genetics.

What switched you on to a career in research?

I was not a bright student, and I didn't know what I wanted to do. After secondary school, I struggled into a 4-year course in Medical Microbiology at Liverpool University, but I wasn't focussed – I enjoyed sport and socialising, mainly. Rather than decide what I wanted to study, I always did the same courses as a friend of mine who had been my roommate. In the last year of our course he told me about a PhD post in Cambridge on influenza virus replication. So, we both applied, but only I was invited for an interview and, remarkably, I got the position.

So, I went to Cambridge. For the first year and a half, I was over-awed. I felt I was stupid and completely lacking in intellectual confidence. And I really struggled at the bench. For instance, I wanted to separate influenza virus RNAs, but I couldn't even get my gels to set for a year. Finally, I managed to produce some good data, and it was this work that showed for the first time that influenza virus replicated in the nucleus, and that it used the host machinery to produce its viral mRNAs and so on. This was halfway through my PhD, and I realised that I had produced something useful – and that I wasn't that stupid. I gained some intellectual confidence, did more experiments that worked and really started to get the bug.

So, I decided I wanted to do a postdoc. Having worked on the nucleus, I decided that I was more interested in the host cell than viruses, and I applied to do a postdoc with someone who's been one of the most influential people in my scientific life. His name was John Bishop. He was a very clever and scary man, a big hotshot at the time, and he was based in Edinburgh. He was working on DNA reassociation kinetics – which basically tells you something about the complexity of nucleic acid molecules. John had applied these approaches to study the complexity of RNA molecules in cell lines, and he'd published a *Nature* article on this (Bishop et al., 1974). When I went to work with him, I decided I wanted to study this in real tissues. I looked at mouse brain,

liver and kidney, worked out the complexity of the RNAs in each tissue, and determined the extent of overlap of specific sets of RNAs in the different tissues. This was eventually published in a *Cell* paper (Hastie and Bishop, 1976), but not until 6 months after I had completed my postdoc and gone to work in the States.

What led you to take a job in the States?

I've hardly ever applied for a job in my life, and my position in the States was no exception. RNA complexity was a hot topic at that time, and someone from Roswell Park Memorial Institute [now called Roswell Park Cancer Institute] in Buffalo, New York, wrote to John Bishop and asked him whether he knew anyone with skills in that area that they might be able to recruit. I had never heard of the Institute, but I went and did the interview. Apparently I gave a terrible seminar, but the discussions afterwards were good, and they offered me the job, which meant I became a group leader in the States at age 28.

Nick Hastie is Director of the MRC Human Genetics Unit at the University of Edinburgh, UK, and Director of the newly formed Institute of Genetics and Molecular Medicine, which includes the Human Genetics Unit. Nick Hastie is a Fellow of the Royal Society, a Fellow of the Royal Society of Edinburgh and a Commander of the British Empire.

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For 7 years in the states, I followed on from work I'd done during my postdoc, looking at liver gene expression during development, identifying new genes in the liver and looking at genome organisation in the mouse. I had two NIH grants and a lovely lab: two postdocs, three students and two technicians. After a while, though, my wife and I began to wonder whether we should come back to the UK – parents were growing older and all that. In 1982, Ed Southern (of the famous Southern blot) phoned to tell me that there was a position available as a group leader at this MRC unit [the Director at the time was Professor John Evans, another major influence in my life]. The unit was very famous for its work on chromosomes, but they were mainly using microscopy and other descriptive techniques, and they wanted someone that would move them into the molecular realm. I couldn't do any lab work, really, so I was very lucky to have some great people come with me from the States – my then-postdoc, Bob Hill, who is now a professor and group leader here at the Human Genetics Unit, and also Richard Meehan, who was at that time a technician and is now also a professor and group leader here.

This move coincided with a shift in your research focus. What encouraged that?
On returning to Edinburgh, I decided that I wanted to get away from mouse gene expression. I had to work on a human problem, and I wanted to work on something that was really interesting biologically. Veronica van Heyningen and I were seduced by deletions on chromosome 11 in patients with a childhood kidney cancer called Wilms' tumour. Children with these deletions also have gonad problems, blindness or aniridia [absence of the iris]. We wanted to use this discovery as a way to find genes that were key for human development. I got very interested in this area, and I'll tell you why in a minute.

At the same time as I was getting into this area, I was working on other aspects of human chromosomes. For instance, Robin Allshire, who was then at the MRC Mammalian Genome Unit here in Edinburgh, came to me with another project. Robin put fission yeast chromosomes into mammalian cells to see if they would replicate – and they did. We used that system to identify human telomeres for the first time. We got it slightly wrong, but we did get there first, and that was published in a *Nature* paper (Allshire et al., 1988). Leading on from that, we studied telomere dynamics and showed in real tissues that telomeres shorten with every year of life – that was also a *Nature* paper and is by far my most cited paper (Hastie et al., 1990).

Telomere biology was a hot area, but my heart wasn't really in it – I was most interested in Wilms' tumour and the *WT1* gene. Why? Well, these tumours develop in children within the first years of life, and the disease is one of the best examples where tumours arise because development has gone awry. Also, inherited mutations in this gene cause not only Wilms' tumour, but severe kidney problems, and sometimes also heart problems or sex reversal. We decided that this had to be a fascinating gene that would tell us about disease as well as normal development. Studying it led us to find many interesting things, including the identification of the *Pax6* gene, which is essential for eye development. We didn't identify the Wilms' tumour gene [*WT1*] – we were just beaten to the chase on that one – but I've done a lot of work on it since.

"My postdocs, and sometimes my students, are often the ones that dictate what I do – I'm a cheerleader, really"

In fact, I've worked on this damn thing for 20 years! However, it's the last 4 years that have got me really excited. That's because we've started to really get at the mechanisms by which these patients get tumours, kidney problems, gonad problems, heart problems and so on. Before recently, I'd never published a mechanistic paper in my life – I'd always worked on quite descriptive studies. It's my recent postdocs (Ofelia Martinez-Estrada, Abdel Essafi and You-Ying Chau) that have really dragged me into looking at mechanisms. My postdocs, and sometimes my students, are often the ones that dictate what I do – I'm a cheerleader, really. I have a few ideas, but they have a lot more.

What does WT1 do?
We've been making some progress recently on the mechanisms by which WT1 acts, and it's looking more interesting all the time. Basically, it looks like WT1 is a tumour suppressor during development, but in the adult, it acts like an oncogene. How does the absence of WT1 cause kidney and heart problems in children? Briefly, our data show that WT1 is essential during development for the mesenchymal-to-epithelial transition that gives rise to the epithelial cells of the nephron. When WT1 is non-functional, this transition doesn't happen, and mesenchymal tumours occur. In the heart, however, the protein does something quite different. Here, it's required for an epithelial-to-mesenchymal transition that gives rise to heart progenitor cells. Some of this is described in our recent *Nature Genetics* paper (Martínez-Estrada et al., 2010). What's more, we've found that the genes activated by WT1 in the kidney are repressed by WT1 in the heart, and vice versa. This is partly described in a *Developmental Cell* paper from last year (Essafi et al., 2011). In the same study, we discovered that WT1 can reciprocally activate or repress a specific region of chromatin to set up either an epithelial or mesenchyme state. We call this feature 'flip-flop'.

So, that helps to explain what happens during development when *WT1* is deleted. In the adult, however, *WT1* is expressed at high levels in many cancers, including ovarian, breast, bowel and pancreatic, but not in the normal epithelia from which those cancers are derived. What's its role there? Well, this part of our work is exciting me a great deal at the moment – part of the story we just published in *PLoS Genetics* in December (Chau et al., 2011). There's a theory out there that an epithelial-to-mesenchymal transition might be involved in the production of stem cells in a number of compartments, so we wanted to test whether *WT1* might have a role there. We wanted to delete this gene in adult mice, and look at the tissues that are normally affected by cancer when the gene is mutated – we wanted to test whether the stem cells in those tissues were abnormal. So, we knocked out *Wt1* ubiquitously in 10-week-old mature mice using a tamoxifen-Cre system and, within 10 days, the mice died. The kidneys failed, all body fat was lost, the bone became completely osteoporotic, the mice stopped making red blood cells and the exocrine pancreas was 80% lost through apoptosis. All of this happens within 5-8 days of knocking out the gene, and it happens at least in part because deleting *Wt1* disrupts the haematopoietic and mesenchymal stem cell lineages. We don't com-

pletely know how this works yet, but these are very dramatic phenotypes affecting adult tissues in a matter of a few days, and it's really got me excited. I think we're going to learn new things about human disease, stem cells, tissue homeostasis and tissue repair through studying this.

You're also involved in large-scale genetic studies. What do you think has been the most exciting development in this area recently?

In a way, being able to do these huge GWAS has been the most exciting recent development. These studies have told us about the genetic architecture of human traits, and revealed how very complex the genetics of disease susceptibility and complex traits really are. They have told us about new pathways and taught us about pathways we thought we'd already figured out. Paper by paper, these studies are very laborious, of course, because there are so many traits to examine and they just involve piles of data. So, it's essential to go the functional dimension.

In some projects I'm involved with, we're working on isolated populations in Croatia and in Orkney. We do that because we think the genetic structure is simpler and the environment is less variable. There is also more inbreeding, which might allow us to get at recessive genes. It's proved extremely successful. And we don't just want to map a gene of interest, we want to look at function. For example, we mapped a gene that regulates the levels of uric acid in the blood (uric acid is vital for developing gout). In people with high levels of uric acid we found a gene that was reported to encode a fructose transporter. When we looked at it more carefully, we found that it is an extremely efficient urate transporter (Vitart et al., 2008). So, the genetics led us to find a function for this gene that was different from that which had initially been described. We also showed that variation with this gene was associated with susceptibility to gout, which is an increasing problem.

Something exciting that's happened in this unit is the development of a paradigm to explain how very long-distance elements regulate gene expression – these studies are mainly led by Bob Hill, Veronica van Heyningen and David Fitzpatrick. This is important because, when we do GWAS, half of the things we map are in gene deserts, not in genes. That means that a lot of the things that dictate complex human traits are going to be very long-distance chromosome effects. That, to us, is one of the most exciting developments: suggested roles for gene deserts, regulatory elements and chromosomal structure. What we're trying to do here in this unit is put this all together – to combine complex human genetics and chromosome biology to understand not only traits and disease, but also more about the regulation of gene expression.

There are a lot of big projects underway that use whole-exome sequencing. If so much is determined by variation in non-coding regions, won't this approach miss some crucial things?

That's true. But the aim of whole-exome sequencing is to find rare variants with large effect. The larger effect variants will likely affect proteins, whereas regions in gene deserts or regulatory elements are more likely to have small effects on a trait or a disease – they likely contribute, but won't be where the gold is, so to speak. So, we think the place to start, anyway, is exome sequencing.

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If you could start over, what research question or what disease would you address?

If I were brave and could start again, it would be to try to get at the basis of the genetic factors involved in behavioural, psychotic and related diseases. I would work on bipolar disorder, schizophrenia, autism – behavioural and cognitive defects like that. To understand how the brain works is one of the most challenging areas of research, and studying the diseases that affect brain function may provide major insights. The hope would be to try to link genetics to the biology of the brain – I think that would be incredible.

My interest in this area is also personal. Five years ago, my brother had a terrible time with head and neck cancer, and he died eventually. I was OK for about a year after that, but then I became completely neurotic about my health. I fell into a state of major anxiety, and then depression, for 3 or 4 months. I couldn't sleep, I lost all confidence, and I thought I'd never done anything valuable for anybody in science or in my life. This was completely unlike me. But I was lucky – I recovered, just in time for my daughter's wedding. But I'll never forget what it was like, how I couldn't focus on anything, how I lost all of my personality. I got a glimpse into what these problems are like for patients – some people suffer their whole lives from these types of conditions, and they are worse than a physical illness in many ways.

But this area – it's still a Cinderella thing. There's very little money going into mental health research compared with funding for diseases such as cancer and heart disease. Huge amounts of money are needed to take large cohorts of people with various cognitive, behavioural and psychotic problems and do sequencing and all the rest, and then bring that together with biology. For example, we are about to apply exome sequencing on a defined population of 24,000 Scottish people to find variants associated with depression or cognitive variation.

What can you tell us that our readers would be surprised to know about you?

Well, one thing that not many people know about me is that I once considered a career in singing, as a bass baritone. When I was in Cambridge, I was offered a place in the famous King's College Choir. I decided not to go that route, but I did continue to sing solos over the years. Another thing you might not guess is that I go to the gym four or five times a week – I love Body Combat and Body Pump and all of those sorts of things. I think exercise is so important, and I only started up again 5 years ago after many years of not exercising – it's something everyone should remember.

I would like to close by thanking all of the wonderful people who have worked with me over the years, including technicians, postdocs, students and my long-suffering PA, Katie Browne, and her assistant, Brenda Henderson.

DMM greatly appreciates Nick Hastie's willingness to share his unique thoughts and

experiences. He was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee. Excerpts from this interview can be heard in the podcast associated with DMM Vol. 5, Issue 2 at http://www.biologists.com/DMM/podcasts/index.html.

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